UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,491	12/16/1999	Sheng-Yung Pai Chang	RPA1002	8931

22829 7590 03/27/2002

ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA, CA 94501

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/27/2002

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/465,491	Applicant(s) CHANG ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 28-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 28-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed February 20, 2002. Currently, claims 21, 28-45 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 20, 2002 has been entered.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21, 33, 34, 38, 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying the presence of cancerous cells in a human sample using primers which hybridize within exon 8, does not reasonably provide enablement for primers which hybridize within exon 8 or downstream of exon 8. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims have been amended to broaden the scope of the claims to encompass embodiments set forth by the specification as unpredictable, namely using primers which hybridize outside of exon 8.

The specification teaches "the methods of the invention involve amplifying a target hTERT mRNA sequence using a pair of primers in which one primer hybridizes to a sequence within exon 8, which is a subregion of the beta region, and the other primer hybridizes to a sequence outside the beta region, preferably within exon 6, upstream of the beta region, and quantitatively detection the formation of amplification products. Such a primer pair has the property that the amplified mRNA corresponds to primarily mRNA that encodes an active hTERT protein." (page 3, lines 20-25). "As seen in lanes 6-9, an estimate of telomerase activity based on a quantitation of hTERT mRNA expression would be inaccurate because only a fraction of the mRNA in the sample encodes an active hTERT protein" (page 23, lines 11-13). "This unpredictability can be eliminated by selectively amplifying only hTERT mRNA that encodes an active hTERT protein, as described in the following example" (page 23, lines 20-23). "This uniformity provided by the primers of the invention results in more consistent and accurate quantitative estimates when used in the quantitative methods described in the following examples" (page 25, lines 20-23).

Thus, the skilled artisan would not be able to use the invention as broadly as claimed based upon applicant's own teachings that primers outside exon 8 lead to

unpredictable results. The skilled artisan would be required to determine and invent a new method which would allow him to obtain predictable results using primers which the specification teaches are unpredictable. Therefore, using primers wherein at least one of the primers is not within exon 8 is unpredictable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 21, 33, 34, 38, 42, are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 21, 33, 34, 38, 42 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 6 filed December 21, 2000. In that paper, applicant has stated "One of the critical aspect of the methods is the use of a primer that hybridizes within exon 8, which is a particular sub-region within the beta region" (page 10), and this statement indicates that the invention is different from what is defined in the claim(s) because the claims are not limited to the "critical aspect of the method". Furthermore, in Papter No. 9, filed June 15, 2001, page 14, applicant's have provided a comparison between Hisatomi and the instant invention to illustrate that a critical aspect of the invention is the position of the primers such that they are capable of selectively amplifying hTERT mRNA containing the beta region. The specification additionally provides that primers outside these regions lead to unpredictable results (see Enablement rejection above).

6. Claims 21, 28-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 21, 28-45 are indefinite over the recitation of "a first primer capable of hybridizing" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited primers have the potential to hybridize within exon 8 or downstream of exon 8 or do in fact hybridize to the region. Amendment of the claim to read, for example, "which hybridizes within (region X)" would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claim 21, 28, 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Nakamura-2 (Molecular Carcinogenesis, Vol 26, pages 312-320, 1999).

Nakamura-2 teaches that telomerase activity was examined quantitatively in gartrointestinal tissues by using the hybridization protection assay combined with the telomeric repeat amplification protocol (TRAP) to assess the diagnostic utility of measuring telomerase activity to determine the relationship between telomerase activity and human telomerase reverse transcriptase (hTERT expression) (abstract). The

methods of Nakamura for measuring expression by RT-PCR used primers in exon 5/6 and in exon 10, namely primers TERT/U1513 and TERT/L1982 (page 314, col 1). Nakamura teaches that "the different in hTERT expression levels between cancerous and noncancerous tissues was less the mean expression level was higher in cancerous tissues than in noncancerous tissues" (pg 317, col. 1). Thus, Nakamura necessarily has quantified the hTERT levels. Moreover, using the hTERT expression levels and the plots of Figure 4, the telomerase activity may be quantitated. Finally, as provided in Figure 4, cancerous cells may be identified by their hTERT activity. Nakamura also teaches that more than "twice higher hTERT expression in tumor than in non-tumor samples from the same patient was observed (pg 319-320).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 21, 31, 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cech et al. (US Pat. 6,166,178, December 2000) in view of Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997).

This rejection is directed to the broad claims which require primers within exon 8 and upsteam of exon 8.

Cech et al. (herein referred to as Cech) teaches a wide variety of assays for hTERT. Cech teaches that hTERT gene products are usually elevated in immortal human cells relative to most normal cells (col 98, lines 3-4). Cech teaches that diagnostic methods of the method entail determining whether a human TRT gene product is present in a biological sample from a patient (col 98, linces 24-26). The abundance of hTRT gene product in a biological sample from a patient is determine and compared to the abundance in a control sample such as normal cells or tissues (col 98, lines 28-30). Quantities of hTRT gene produce may be measured. Cech teaches that measuring hTRT gene products in two or more different samples, will be useful to have a common basis of comparison for the two samples (col 104, lines 29-32). Cech teaches preparing nucleic acids for amplification based assays such that all or part of an hTRT gene is amplified (col 106, lines 44-45). Cech teaches that a wide variety of primers and probes for detecting hTRT genes are provided and characterizes the general structure of primers to be about 14-25 bases in length (col 106). Cech teaches that one of ordinary skill having reviewed the present disclosure will be able using routine methods select primers that amplify all or any portion of the hTRT gene (col 107). Col 5-6 also detail numerous methods for comparison of expression levels and diagnosis of cancer based upon a greater quantity of hTRT compared to normal samples (see especially col 6, lines 30-40). Cech teaches kits comprising primers (col. 119).

It is not clear whether Cech teaches a primer within exon 8 and upstream of exon 8.

However Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Cech with the primers of Kilian for detecting expression levels of hTERT. The skilled artisan would have been motivated to have performed the method of Cech using the primers taught by Kilian because Kilian illustrates the primers amplify hTERT allow detection of hTRT. Cech would have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present such that a value of hTERT mRNA may be determined. Quantification of mRNA after separation on gels, at the time the invention was made, was a well known method which provided information regarding transcriptional activity of the mRNA and may be used to study the expression of one gene relative to another gene. The ordinary artisan would have realized based

upon the teachings of Kilian that hTERT is differentially expressed in normal and tumor tissue, that expression levels of hTERT may be used to identify cancerous cells (page 2014, col 1, Figure 2). Therefore, determining the presence of cancerous cells using the methods of Cech with the primers of Kilian would have been provided an accurate means of determining the expression level of hTERT.

9. Claims 28-30, 32, 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cech et al. (US Pat. 6,166,178, December 2000) in view of Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

This rejection is directed to methods using primers of specific sequences and regions.

Cech et al. (herein referred to as Cech) teaches a wide variety of assays for hTERT. Cech teaches that hTERT gene products are usually elevated in immortal human cells relative to most normal cells (col 98, lines 3-4). Cech teaches that diagnostic methods of the method entail determining whether a human TRT gene product is present in a biological sample from a patient (col 98, linces 24-26). The abundance of hTRT gene product in a biological sample from a patient is determine and compared to the abundance in a control sample such as normal cells or tissues (col 98, lines 28-30). Quantities of hTRT gene produce may be measured. Cech teaches that measuring hTRT gene products in two or more different samples, will be useful to have a common basis of comparison for the two samples (col 104, lines 29-32). Cech

teaches preparing nucleic acids for amplification based assays such that all or part of an hTRT gene is amplified (col 106, lines 44-45). Cech teaches that a wide variety of primers and probes for detecting hTRT genes are provided and characterizes the general structure of primers to be about 14-25 bases in length (col 106). Cech teaches that one of ordinary skill having reviewed the present disclosure will be able using routine methods select primers that amplify all or any portion of the hTRT gene (col 107). Col 5-6 also detail numerous methods for comparison of expression levels and diagnosis of cancer based upon a greater quantity of hTRT compared to normal samples (see especially col 6, lines 30-40). Cech teaches kits comprising primers (col. 119).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Cech nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Cech with the primers of Kilian for detecting expression levels of hTERT. The skilled artisan would have been motivated to have performed the method of Cech using the primers taught by Kilian because Kilian illustrates the primers allow amplification of hTERT. Cech would have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present such that a value of hTERT mRNA may be determined. Quantification of mRNA after separation on gels, at the time the invention was made, was a well known method which provided information regarding transcriptional activity of the mRNA and may be used to study the expression of one gene relative to another gene. The ordinary artisan would have realized based upon the teachings of Kilian that hTERT is differentially expressed in normal and tumor tissue, that expression levels of hTERT may be used to identify cancerous cells (page 2014, col 1, Figure 2). Therefore, determining the presence of cancerous cells using the methods of Cech with the primers of Kilian would have been provided an accurate means of determining the expression level of hTERT.

Moreover, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for

detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were functional equivalents to those provided by Kilian. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by

applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gcc[redacted]ggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcc[redacted]tcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. Absent

factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

10. Claims 21, 28-32, 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hisatomi et al. (International J. of Oncology, Vol 14, pg 727-732, 1999) further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained.

However, Hisatomi et al. (herein referred to as Hisatomi) teaches that levels of hTERT mRNA was investigated with regard to tumor tissue and non-cancerous tissues. The difference of hTERT mRNA level was highly significant between the tumor tissue and the non-cancerous liver tissue (abstract). Moreover, a strong correlation between the levels of hTERT mRNA and that of telomerase activity in HCC was observed (abstract). HTERT mRNA was amplifies using primers, a real-time PCR system provided the essential information to quantify the initial target copy number (pg 728, col. 1-2). The levels of hTERT mRNA were provided (pg 728, col. 2) and significance was shown. As seen in Figure 2, quantification of hTERT mRNA was plotted relative to the tumor or non-tumor status of the tissue (limitations of Claim 1, 21). A cutoff was provided at 1.16 such that hTERT above this "threshold" were at risk for being cancerous. As seen in Figure 4, a correlation between the quantification of hTERT mRNA and telomerase activity is provided such that telomerase activity may be assessed from the mRNA of hTERT (limitations of Claim 8).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hisatomi nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were functional equivalents to those provided by Kilian. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary

artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtacttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcc[redacted]ttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and

the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Moreover, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Hisatomi which specifically quantifies the RNA expression level in log copies/ug total RNA. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilization in expression level comparison as taught by Hisatomi. The skilled artisan would have been motivated to have quantitated the results from Kilian for analysis as provided by Hisatomi. Hisatomi teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics such that if hTERT level is greater than the "threshold" the cells were considered cancerous. Hisatomi illustrates the importance of obtaining a numerical quantity for the amount of hTERT mRNA present in a sample.

11. Claims 21, 28-32, 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-

2019, 1997) in view of Meyerson et al. (Cell, Vol 90, pg 785-795, August 1997) further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained. Kilian also does not teach identifying the presence of cancerous cells by hTERT quantitiy.

However, Meyerson teaches hEST2 (hTERT) is expressed at high levels in primary tumors, cancer cell lines, and telomerase-positive tissues, but is undetectalbe in telomerase negative cell lines (abstract). Meyerson teaches that activation of telomerase also appears to be a major step in the progression of human cancers (pg 786, col. 1). Meyerson teaches that "we analyzed the expression levels of hEST2

mRNA in various cell types, using both RNA Northern hybridizations and Rnase protection assays to do so" (pg 789, col. 2). Thus, Meyerson necessarily has quantitated the mRNA of hEST2 since an expression level was obtained. Moreover as seen in Figure 4, hEST2 mRNA was strongly expressed in a variety of cancer cell lines (pg 790, col. 1).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Myerson nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would

attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were functional equivalents to those provided by Kilian. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gcc[redacted]ggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcc[redacted]ttcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Moreover, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Meyerson which quantifies the RNA expression level. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilization in expression level comparison as taught by Meyerson. The skilled artisan would have been motivated to have quantitated the

results from Kilian for analysis as provided by Meyerson. Meyerson teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics.

12. Claims 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Nakamura et al (Genbank Accession Number AF015950, August 1997) and in further view of Stratagene Catalog (1988).

This rejection is directed to kit claims containing primer pairs.

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Further, with regard to the limitation that the kits contain instructions for identifying cancerous cells, the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit.

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7

nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R (limitations of Claim 3). Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hudkins nor Kilian specifically teach the primers and probes of the instant case in a kit.

Nakamura however teaches the entire sequence of the hTERT gene.

Stratagene teaches gene characterization kits.

Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would

attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were functional equivalents to those provided by Kilian. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids which lacked the deletion of exon 7 and 8, the B-deletion. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gcc[redacted]ggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggcc[redacted]tcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura and placed the primers and probes into a kit. The ordinary artisan would be motivated to have packaged the primers into a kit to reduce waste, save money, increase quality control and save time, as taught by Stratagene.

Conclusion

13. No claims allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
March 20, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600